clear of art

4/4 closest prior art

3/4 current appl.

10/541,387A Yong Chu 8/9/2007

$%^STN;HighlightOn=;HighlightOff=;

Connecting via Winsock to STN

Welcome to STN International! Enter x:x

LOGINID:ssptaylc1626

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS 1		Web Page for STN Seminar Schedule - N. America
NEWS 2	MAY 01	New CAS web site launched
NEWS 3	MAY 08	CA/CAplus Indian patent publication number format defined
NEWS 4	MAY 14	RDISCLOSURE on STN Easy enhanced with new search and display fields
NEWS 5	MAY 21	BIOSIS reloaded and enhanced with archival data
NEWS 6	MAY 21	TOXCENTER enhanced with BIOSIS reload
NEWS 7	MAY 21	CA/CAplus enhanced with additional kind codes for German patents
NEWS 8	MAY 22	CA/CAplus enhanced with IPC reclassification in Japanese patents
NEWS 9	JUN 27	CA/CAplus enhanced with pre-1967 CAS Registry Numbers
NEWS 10	JUN 29	STN Viewer now available
NEWS 11	JUN 29	STN Express, Version 8.2, now available
NEWS 12	JUL 02	LEMBASE coverage updated
NEWS 13	JUL 02	LMEDLINE coverage updated
NEWS 14	JUL 02	SCISEARCH enhanced with complete author names
NEWS 15	JUL 02	CHEMCATS accession numbers revised
NEWS 16	JUL 02	CA/CAplus enhanced with utility model patents from China
NEWS 17	JUL 16	CAplus enhanced with French and German abstracts
NEWS 18	JUL 18	CA/CAplus patent coverage enhanced
NEWS 19	JUL 26	USPATFULL/USPAT2 enhanced with IPC reclassification
NEWS 20	JUL 30	USGENE now available on STN
NEWS 21	AUG 06	CAS REGISTRY enhanced with new experimental property tags
NEWS 22	AUG 06	BEILSTEIN updated with new compounds
NEWS 23	AUG 06	FSTA enhanced with new thesaurus edition

NEWS EXPRESS 29 JUNE 2007: CURRENT WINDOWS VERSION IS V8.2,
CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
AND CURRENT DISCOVER FILE IS DATED 05 JULY 2007.

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* * * * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 11:39:14 ON 09 AUG 2007

=> file reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'REGISTRY' ENTERED AT 11:39:33 ON 09 AUG 2007
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STRUCTURE FILE UPDATES: 8 AUG 2007 HIGHEST RN 944313-22-8
DICTIONARY FILE UPDATES: 8 AUG 2007 HIGHEST RN 944313-22-8

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH December 2, 2006

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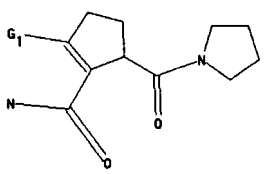
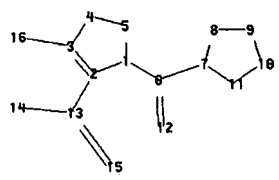
http://www.cas.org/support/stngen/stndoc/properties.html

=>
Uploading C:\Documents and Settings\ychu\Desktop\Case\10541387\10541387A.str





chain nodes :
6 12 13 14 15 16
ring nodes :

1 2 3 4 5 7 8 9 10 11
chain bonds :
1-6 2-13 3-16 6-7 6-12 13-14 13-15
ring bonds :
1-2 1-5 2-3 3-4 4-5 7-8 7-11 8-9 9-10 10-11
exact/norm bonds :
1-2 1-5 2-3 3-4 3-16 4-5 6-7 6-12 7-8 7-11 8-9 9-10 10-11 13-14 13-15

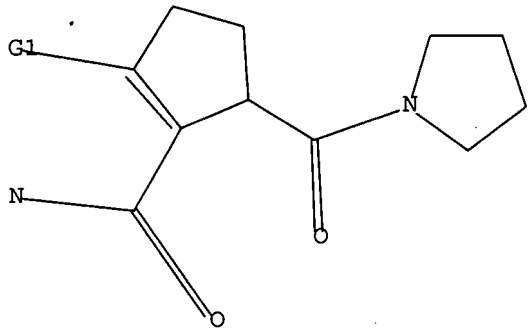
exact bonds :
1-6 2-13

G1:H,CH3,Et

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:CLASS 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:CLASS 13:CLASS 14:CLASS 15:CLASS 16:CLASS

L1 STRUCTURE UPLOADED

=> d
L1 HAS NO ANSWERS
L1 STR



G1 H,Me,Et

Structure attributes must be viewed using STN Express query preparation.

=> a l1
A IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> s l1
SAMPLE SEARCH INITIATED 11:39:58 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 270 TO ITERATE

100.0% PROCESSED 270 ITERATIONS 1 ANSWERS
SEARCH TIME: 00.00.01

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FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:          4415 TO     6385
PROJECTED ANSWERS:                1 TO       80

L2             1 SEA SSS SAM L1

=>
Connection closed by remote host

Connecting via Winsock to STN



Welcome to STN International!  Enter x:x

LOGINID:ssptaylc1626

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2


* * * * * * * * * *   Welcome to STN International   * * * * * * * * * *

 NEWS  1           Web Page for STN Seminar Schedule - N. America
 NEWS  2  MAY 01   New CAS web site launched
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                   fields
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                   patents
 NEWS  8  MAY 22   CA/CAplus enhanced with IPC reclassification in Japanese
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 NEWS  9  JUN 27   CA/CAplus enhanced with pre-1967 CAS Registry Numbers
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 NEWS 15  JUL 02   CHEMCATS accession numbers revised
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 NEWS 20  JUL 30   USGENE now available on STN
 NEWS 21  AUG 06   CAS REGISTRY enhanced with new experimental property tags
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 NEWS EXPRESS  29 JUNE 2007:  CURRENT WINDOWS VERSION IS V8.2,
               CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 05 JULY 2007.

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 NEWS LOGIN    Welcome Banner and News Items
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* * * * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 14:15:01 ON 09 AUG 2007

=> file reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'REGISTRY' ENTERED AT 14:15:28 ON 09 AUG 2007
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STRUCTURE FILE UPDATES: 8 AUG 2007 HIGHEST RN 944313-22-8
DICTIONARY FILE UPDATES: 8 AUG 2007 HIGHEST RN 944313-22-8

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TSCA INFORMATION NOW CURRENT THROUGH December 2, 2006

Please note that search-term pricing does apply when conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

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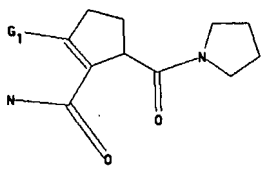
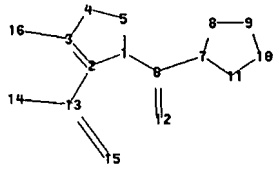
Uploading C:\Documents and Settings\ychu\Desktop\Case\10541387\10541387A.str





chain nodes :
6 12 13 14 15 16
ring nodes :
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1-6 2-13 3-16 6-7 6-12 13-14 13-15
ring bonds :
1-2 1-5 2-3 3-4 4-5 7-8 7-11 8-9 9-10 10-11
exact/norm bonds :
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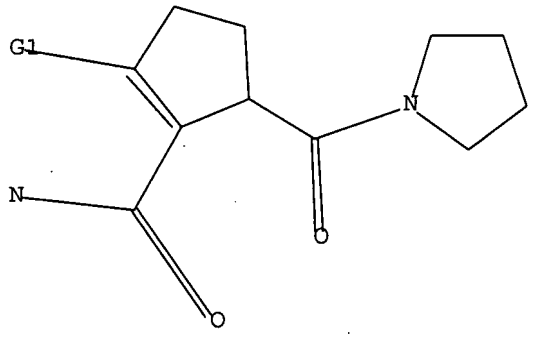
exact bonds :
1-6 2-13

G1:H,CH3,Et

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:CLASS 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:CLASS 13:CLASS 14:CLASS 15:CLASS 16:CLASS

L1 STRUCTURE UPLOADED

=> d
L1 HAS NO ANSWERS
L1 STR



G1 H,Me,Et

Structure attributes must be viewed using STN Express query preparation.

=> s l1
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SAMPLE SCREEN SEARCH COMPLETED - 270 TO ITERATE

100.0% PROCESSED 270 ITERATIONS 1 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**

BATCH **COMPLETE**
PROJECTED ITERATIONS: 4415 TO 6385
PROJECTED ANSWERS: 1 TO 80

L2 1 SEA SSS SAM L1

=> s l1 full
FULL SEARCH INITIATED 14:15:50 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 5159 TO ITERATE

100.0% PROCESSED 5159 ITERATIONS 17 ANSWERS
SEARCH TIME: 00.00.01

L3 17 SEA SSS FUL L1

=> file caplus
COST IN U.S. DOLLARS SINCE FILE ENTRY TOTAL SESSION
FULL ESTIMATED COST 172.10 172.31

FILE 'CAPLUS' ENTERED AT 14:15:54 ON 09 AUG 2007
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FILE COVERS 1907 - 9 Aug 2007 VOL 147 ISS 7
FILE LAST UPDATED: 8 Aug 2007 (20070808/ED)

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=> s l3
L4 4 L3

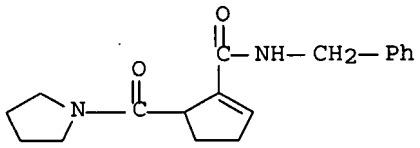
=> d ibib abs hitstr tot

L4 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:1001130 CAPLUS Full-text
DOCUMENT NUMBER: 146:2892
TITLE: An introduction of a pyridine group into the structure of prolyl oligopeptidase inhibitors
AUTHOR(S): Jarho, Elina M.; Venaelaeinen, Jarkko I.; Juntunen, Juha; Yli-Kokko, A. Leena; Vepsaelaeinen, Jouko; Christiaans, Johannes A. M.; Forsberg, Markus M.; Jaervinen, Tomi; Maennistoe, Pekka T.; Wallen, Erik A. A.
CORPORATE SOURCE: Department of Pharmaceutical Chemistry, University of

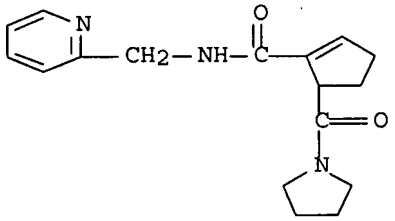
Kuopio, Kuopio, FI-70211, Finland
SOURCE: Bioorganic & Medicinal Chemistry Letters (2006), 16(21), 5590-5593
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 146:2892

AB A series of ionizable prolyl oligopeptidase inhibitors were developed through the introduction of a pyridyl group to the P3 position of the prolyl oligopeptidase inhibitor structure. The study was performed on previously developed prolyl oligopeptidase inhibitors with proline mimetics at the P2 position. The 3-pyridyl group resulted in equipotent compds. as compared to the parent compds. It was shown that the pyridyl group improves water soly. and, in combination with a 5(R)-tert-butyl-L- prolyl group at the P2 position, good lipophilicity can be achieved.

IT 725265-77-0
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(introduction of pyridine group into the structure of prolyl oligopeptidase inhibitors)
RN 725265-77-0 CAPLUS
CN 1-Cyclopentene-1-carboxamide, N-(phenylmethyl)-5-(1-pyrrolidinylcarbonyl)- (CA INDEX NAME)



IT 914615-93-3P 914615-94-4P 914615-95-5P
914615-96-6P 914615-97-7P 914615-98-8P
914615-99-9P
RL: BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(introduction of pyridine group into the structure of prolyl oligopeptidase inhibitors)
RN 914615-93-3 CAPLUS
CN 1-Cyclopentene-1-carboxamide, N-(2-pyridinylmethyl)-5-(1-pyrrolidinylcarbonyl)- (CA INDEX NAME)



RN 914615-94-4 CAPLUS
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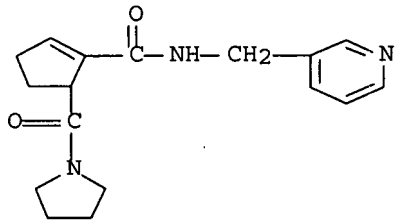
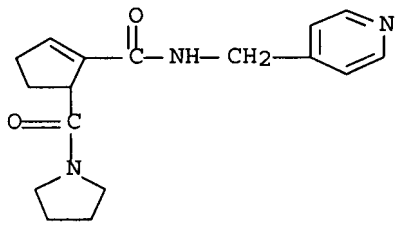
pyrrolidinylcarbonyl)- (CA INDEX NAME)



RN 914615-95-5 CAPLUS
CN 1-Cyclopentene-1-carboxamide, N-(4-pyridinylmethyl)-5-(1-pyrrolidinylcarbonyl)- (CA INDEX NAME)



RN 914615-96-6 CAPLUS
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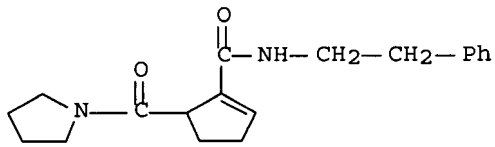

RN 914615-97-7 CAPLUS
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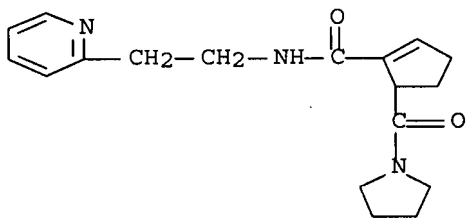
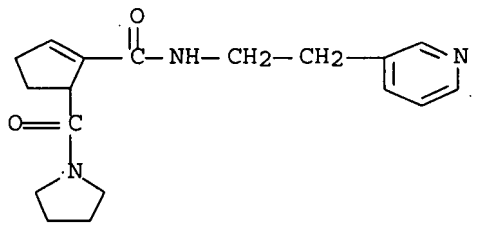
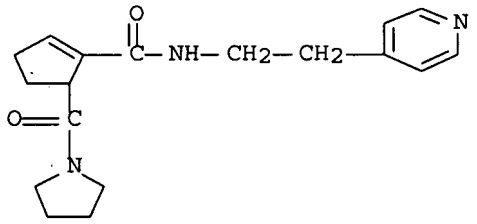


RN 914615-98-8 CAPLUS
CN 1-Cyclopentene-1-carboxamide, N-[2-(3-pyridinyl)ethyl]-5-(1-pyrrolidinylcarbonyl)- (CA INDEX NAME)



RN 914615-99-9 CAPLUS
CN 1-Cyclopentene-1-carboxamide, N-[2-(4-pyridinyl)ethyl]-5-(1-pyrrolidinylcarbonyl)- (CA INDEX NAME)



REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

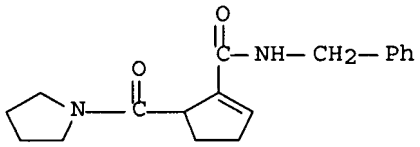
L4 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:800210 CAPLUS Full-text
DOCUMENT NUMBER: 141:421630
TITLE: A Cyclopent-2-enecarbonyl Group Mimics Proline at the P2 Position of Prolyl Oligopeptidase Inhibitors
AUTHOR(S): Jarho, Elina M.; Venaelaeinen, Jarkko I.; Huuskonen, Juhani; Christiaans, Johannes A. M.; Forsberg, Markus M.; Jaervinen, Tomi; Gynther, Jukka; Maennistoe, Pekka T.; Wallen, Erik A. A.
CORPORATE SOURCE: Department of Pharmaceutical Chemistry, Department of Pharmacology and Toxicology, University of Kuopio, Kuopio, FI-70211, Finland
SOURCE: Journal of Medicinal Chemistry (2004), 47(23), 5605-5607
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 141:421630

AB With the aim to replace the natural amino acid proline by a proline mimetic structure, a cyclopent-2-enecarbonyl moiety was studied at the P2 position of prolyl oligopeptidase (POP) inhibitors. The cyclopent-2-enecarbonyl moiety

proved to be an excellent proline mimetic at the P2 position of POP inhibitors. The replacement is particularly useful when increased lipophilicity is needed.

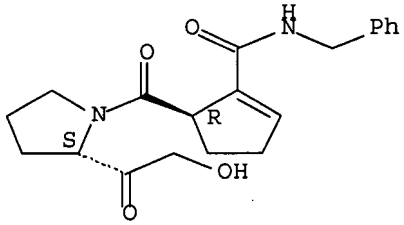
IT 725265-77-0P 796874-93-6P 796874-94-7P
RL: BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(cyclopent-2-enecarbonyl group mimics proline at P2 position of prolyl oligopeptidase inhibitors)

RN 725265-77-0 CAPLUS
CN 1-Cyclopentene-1-carboxamide, N-(phenylmethyl)-5-(1-pyrrolidinylcarbonyl)- (CA INDEX NAME)



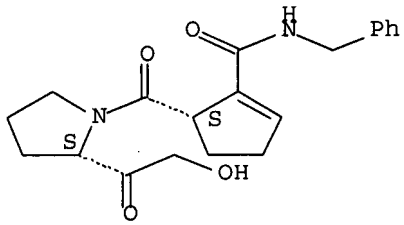
RN 796874-93-6 CAPLUS
CN 1-Cyclopentene-1-carboxamide, 5-[[(2S)-2-(hydroxyacetyl)-1-pyrrolidinyl]carbonyl]-N-(phenylmethyl)-, (5R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



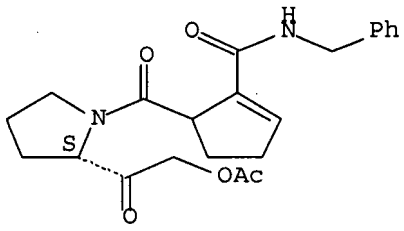
RN 796874-94-7 CAPLUS
CN 1-Cyclopentene-1-carboxamide, 5-[[(2S)-2-(hydroxyacetyl)-1-pyrrolidinyl]carbonyl]-N-(phenylmethyl)-, (5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 725265-75-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(cyclopent-2-enecarbonyl group mimics proline at P2 position of prolyl oligopeptidase inhibitors)
RN 725265-75-8 CAPLUS
CN 1-Cyclopentene-1-carboxamide, 5-[[(2S)-2-[(acetyloxy)acetyl]-1-pyrrolidinyl]carbonyl]-N-(phenylmethyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

Current app.

L4 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:589531 CAPLUS Full-text
DOCUMENT NUMBER: 141:140770
TITLE: Preparation of proline derivatives having prolyl oligopeptidase inhibitory activity
INVENTOR(S): Gynther, Jukka; Wallen, Erik; Jarho, Elina; Maennistoe, Pekka; Forsberg, Markus; Poso, Antti; Christiaans, Johannes; Venaelaeinen, Jarkko; Vepsaelaeinen, Jouko; Saarinen, Taija; Jaervinen, Tomi
PATENT ASSIGNEE(S): Orion Corporation, Finland
SOURCE: PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004060862	A2	20040722	WO 2004-FI1	20040102
WO 2004060862	A3	20041125		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ				
AU 2004203788	A1	20040722	AU 2004-203788	20040102
CA 2511856	A1	20040722	CA 2004-2511856	20040102
EP 1581489	A2	20051005	EP 2004-700047	20040102
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2004006618	A	20051206	BR 2004-6618	20040102
CN 1747930	A	20060315	CN 2004-80003468	20040102
JP 2006516557	T	20060706	JP 2006-500146	20040102

ZA 2005005183	A	20060426	ZA 2005-5183		20050627
IN 2005KN01260	A	20061110	IN 2005-KN1260		20050628
MX 2005PA07262	A	20050908	MX 2005-PA7262		20050701
NO 2005003726	A	20050928	NO 2005-3726		20050803
US 2006229254	A1	20061012	US 2006-541387		20060509
PRIORITY APPLN. INFO.:			FI 2003-14	A	20030103
			WO 2004-FI1	W	20040102

OTHER SOURCE(S): MARPAT 141:140770

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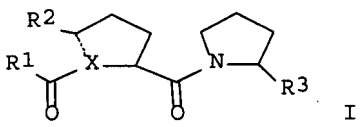


I

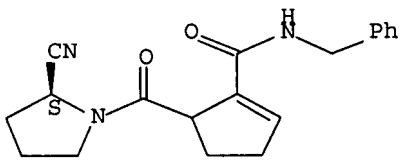
AB The invention provides compds. I [X is N or C; R1 is (un)substituted alkyl, alkenyl, a carbocyclic or heterocyclic ring; R2 is H or (un)substituted alkyl, alkenyl or alkynyl; R3 is H, cyano, hydroxy, oxo, halo, alkyl, alkoxy, aryl, aryloxy, arylalkoxy, amino, alkylamino, arylamino, arylalkylamino, cycloalkyl, heterocyclyl, carboxy, acyl, etc., where the alkyl groups may be substituted; when X is N, the dotted line represents a single bond and R2 is not H; when X is C, the dotted line represents a double bond and R2 is H] or their pharmaceutically-acceptable salts or esters having prolyl oligopeptidase inhibitory activity for the treatment of neurodegenerative diseases such as Alzheimer's disease and senile dementia. Thus, 2-(benzylcarbamoyl)cyclopent-2-enecarboxylic acid 2-(S)-cyanopyrrolidine amide was prepd. from cyclopent-2-ene-1,2- dicarboxylic acid 1-Me ester and proline Me ester and showed IC50 = 0.38 nM for inhibition of pig brain prolyl oligopeptidase.

IT 725265-74-7P 725265-76-9P 725265-77-0P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of proline derivs. having prolyl oligopeptidase inhibitory activity)

RN 725265-74-7 CAPLUS

CN 1-Cyclopentene-1-carboxamide, 5-[[(2S)-2-cyano-1-pyrrolidinyl]carbonyl]-N-(phenylmethyl)- (9CI) (CA INDEX NAME)

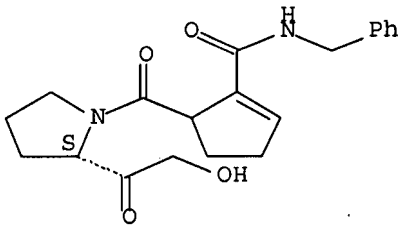
Absolute stereochemistry.



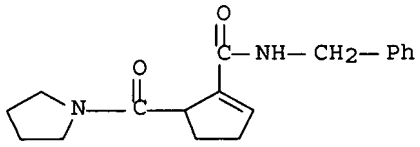
RN 725265-76-9 CAPLUS

CN 1-Cyclopentene-1-carboxamide, 5-[[(2S)-2-(hydroxyacetyl)-1-pyrrolidinyl]carbonyl]-N-(phenylmethyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

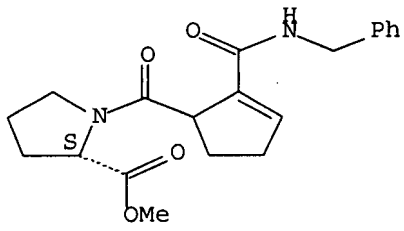


RN 725265-77-0 CAPLUS
CN 1-Cyclopentene-1-carboxamide, N-(phenylmethyl)-5-(1-pyrrolidinylcarbonyl)-
(CA INDEX NAME)



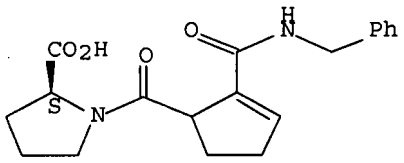
IT 725265-71-4P 725265-72-5P 725265-73-6P
725265-75-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
(Reactant or reagent)
(prepn. of proline derivs. having prolyl oligopeptidase inhibitory
activity)
RN 725265-71-4 CAPLUS
CN L-Proline, 1-[[2-[[(phenylmethyl)amino]carbonyl]-2-cyclopenten-1-
yl]carbonyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



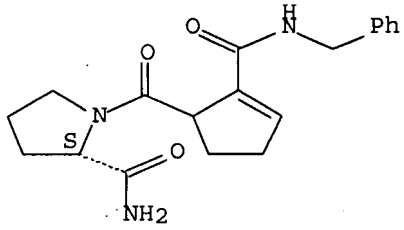
RN 725265-72-5 CAPLUS
CN L-Proline, 1-[[2-[[(phenylmethyl)amino]carbonyl]-2-cyclopenten-1-
yl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



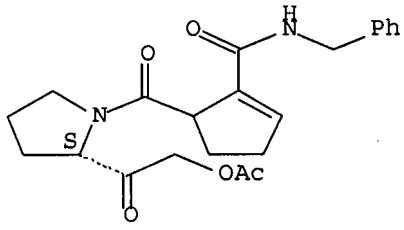
RN 725265-73-6 CAPLUS
CN 2-Pyrrolidinecarboxamide, 1-[[2-[[(phenylmethyl)amino]carbonyl]-2-cyclopenten-1-yl]carbonyl]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 725265-75-8 CAPLUS
CN 1-Cyclopentene-1-carboxamide, 5-[[(2S)-2-[(acetyloxy)acetyl]-1-pyrrolidinyl]carbonyl]-N-(phenylmethyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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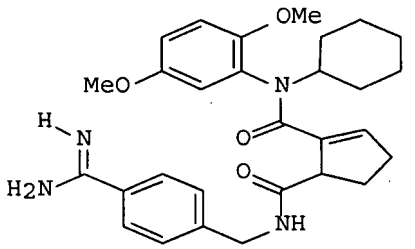
Pub date 3/27/03

L4 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:170639 CAPLUS Full-text
DOCUMENT NUMBER: 138:337715
TITLE: Synthesis of Novel Thrombin Inhibitors. Use of Ring-Closing Metathesis Reactions for Synthesis of P2 Cyclopentene- and Cyclohexenedicarboxylic Acid Derivatives
AUTHOR(S): Thorstensson, Fredrik; Kvarnstroem, Ingemar; Musil, Djordje; Nilsson, Ingemar; Samuelsson, Bertil
CORPORATE SOURCE: Department of Chemistry, Linkoeping University, Linkoeping, S-581 83, Swed.
SOURCE: Journal of Medicinal Chemistry (2003), 46(7),

1165-1179
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 138:337715
GI



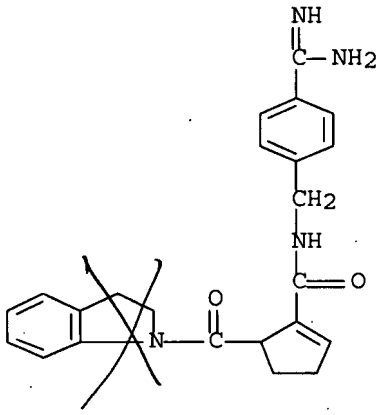
I

AB (amidino)benzylaminocarbonyl-substituted cyclopentenylcarboxamides and cyclohexenylcarboxamides such as I are prepd. as human .alpha.-thrombin inhibitors using ring-closing olefin metathesis in the presence of the second-generation Grubbs olefin metathesis catalyst as the key step. .alpha.,.beta.-Unsatd. carboxylic acids undergo ring-closing olefin metathesis in the presence of the second-generation Grubbs olefin metathesis catalyst to provide cyclopentenecarboxylic and cyclohexenecarboxylic acids in 85-98% yields; use of the first-generation Grubbs olefin metathesis catalyst gives no product with the free acids, and gives product in low yields only when the carboxylic acid moieties are reduced. Coupling of the unsatd. acids with either amines or (Cbz-amidino)benzylamine dihydrochloride followed by hydrolysis of an ester substituent and coupling with either (Cbz-amidino)benzylamine dihydrochloride or amines provides .alpha.-thrombin inhibitors such as I. Amidation reactions of the substrate acids with hindered aryl amines only proceed using BOP chloride as the coupling reagent at elevated temps. in DMF; other coupling reagents give products either in decreased yields or not at all. Most of the 5-(amidino)benzylaminocarbonyl-2- cyclopentenylcarboxamides inhibit .alpha.-thrombin with IC50 values of 0.1-10 .mu.M while most of the isomeric cyclopentenylcarboxamides and the cyclohexenylcarboxamides inhibit .alpha.-thrombin with IC50 values between 1-100 .mu.M. The crystal structure of an (amidino)benzylaminocarbonyl- substituted cyclopentenylcarboxamide (IC50 = 220 nM) bound to .alpha.-thrombin is detd.; anal. of the crystal structure led to the design and synthesis of (amidino)benzylaminocarbonyl-substituted cyclopentenylcarboxamides contg. either 3-ethylphenyl or 2,5-dimethoxyphenyl groups with improved binding affinities for .alpha.-thrombin, e.g. I (IC50 = 49 nM).

IT 516491-20-6P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of amidinobenzylaminocarbonyl cyclopentenecarboxamides and cyclohexenecarboxamides as human .alpha.-thrombin inhibitors)

RN 516491-20-6 CAPLUS

CN 1-Cyclopentene-1-carboxamide, N-[[4-(aminoiminomethyl)phenyl]methyl]-5-[(2,3-dihydro-1H-indol-1-yl)carbonyl]- (9CI) (CA INDEX NAME)



closest prior art

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	24.37	196.68

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-3.12	-3.12

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DICTIONARY FILE UPDATES: 8 AUG 2007 HIGHEST RN 944313-22-8

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http://www.cas.org/support/stngen/stndoc/properties.html

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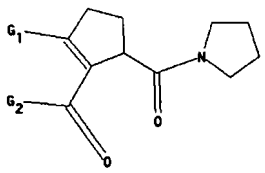

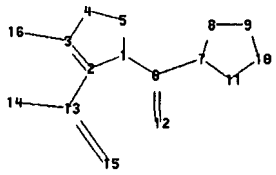

chain nodes :
6 12 13 14 15 16
ring nodes :
1 2 3 4 5 7 8 9 10 11
chain bonds :
1-6 2-13 3-16 6-7 6-12 13-14 13-15
ring bonds :
1-2 1-5 2-3 3-4 4-5 7-8 7-11 8-9 9-10 10-11
exact/norm bonds :
1-2 1-5 2-3 3-4 3-16 4-5 6-7 6-12 7-8 7-11 8-9 9-10 10-11 13-14 13-15

exact bonds :
1-6 2-13

G1:H,CH3,Et

G2:C,O,N,X

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:CLASS 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:CLASS 13:CLASS 14:CLASS 15:CLASS 16:CLASS

L5 STRUCTURE UPLOADED

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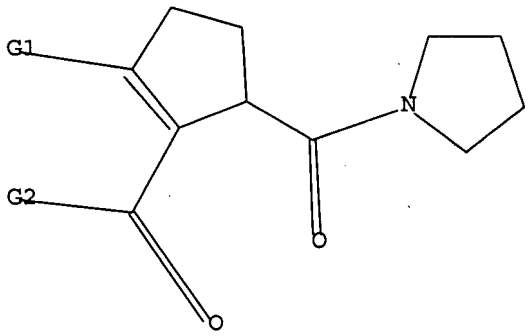
L5 HAS NO ANSWERS
L5 STR



G1 H,Me,Et
G2 C,O,N,X

Structure attributes must be viewed using STN Express query preparation.

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SAMPLE SCREEN SEARCH COMPLETED -      418 TO ITERATE

100.0% PROCESSED      418 ITERATIONS                                  2 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:         7134 TO     9586
PROJECTED ANSWERS:               2 TO      124

L6             2 SEA SSS SAM L5

=> s l5 full
FULL SEARCH INITIATED 14:20:59 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -     8319 TO ITERATE

100.0% PROCESSED     8319 ITERATIONS                                 26 ANSWERS
SEARCH TIME: 00.00.01

L7            26 SEA SSS FUL L5

=> file caplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                      ENTRY    SESSION
FULL ESTIMATED COST                                  172.10     368.78

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                      ENTRY    SESSION
CA SUBSCRIBER PRICE                                    0.00      -3.12

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=> s l7
L8 4 L7

=> d ibib abs tot

L8 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:1001130 CAPLUS Full-text
DOCUMENT NUMBER: 146:2892
TITLE: An introduction of a pyridine group into the structure of prolyl oligopeptidase inhibitors
AUTHOR(S): Jarho, Elina M.; Venaelaeinen, Jarkko I.; Juntunen, Juha; Yli-Kokko, A. Leena; Vepsaelaeinen, Jouko; Christiaans, Johannes A. M.; Forsberg, Markus M.; Jaervinen, Tomi; Maennistoe, Pekka T.; Wallen, Erik A. A.
CORPORATE SOURCE: Department of Pharmaceutical Chemistry, University of Kuopio, Kuopio, FI-70211, Finland
SOURCE: Bioorganic & Medicinal Chemistry Letters (2006), 16(21), 5590-5593
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 146:2892
AB A series of ionizable prolyl oligopeptidase inhibitors were developed through the introduction of a pyridyl group to the P3 position of the prolyl oligopeptidase inhibitor structure. The study was performed on previously developed prolyl oligopeptidase inhibitors with proline mimetics at the P2 position. The 3-pyridyl group resulted in equipotent compds. as compared to the parent compds. It was shown that the pyridyl group improves water soly. and, in combination with a 5(R)-tert-butyl-L- prolyl group at the P2 position, good lipophilicity can be achieved.
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:800210 CAPLUS Full-text
DOCUMENT NUMBER: 141:421630
TITLE: A Cyclopent-2-enecarbonyl Group Mimics Proline at the P2 Position of Prolyl Oligopeptidase Inhibitors
AUTHOR(S): Jarho, Elina M.; Venaelaeinen, Jarkko I.; Huuskonen, Juhani; Christiaans, Johannes A. M.; Forsberg, Markus

M.; Jaervinen, Tomi; Gynther, Jukka; Maennistoe, Pekka T.; Wallen, Erik A. A.

CORPORATE SOURCE: Department of Pharmaceutical Chemistry, Department of Pharmacology and Toxicology, University of Kuopio, Kuopio, FI-70211, Finland

SOURCE: Journal of Medicinal Chemistry (2004), 47(23), 5605-5607
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 141:421630

AB With the aim to replace the natural amino acid proline by a proline mimetic structure, a cyclopent-2-enecarbonyl moiety was studied at the P2 position of prolyl oligopeptidase (POP) inhibitors. The cyclopent-2-enecarbonyl moiety proved to be an excellent proline mimetic at the P2 position of POP inhibitors. The replacement is particularly useful when increased lipophilicity is needed.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:589531 CAPLUS Full-text

DOCUMENT NUMBER: 141:140770

TITLE: Preparation of proline derivatives having prolyl oligopeptidase inhibitory activity

INVENTOR(S): Gynther, Jukka; Wallen, Erik; Jarho, Elina; Maennistoe, Pekka; Forsberg, Markus; Poso, Antti; Christiaans, Johannes; Venaelaeinen, Jarkko; Vepsaelaeinen, Jouko; Saarinen, Taija; Jaervinen, Tomi

PATENT ASSIGNEE(S): Orion Corporation, Finland

SOURCE: PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004060862	A2	20040722	WO 2004-FI1	20040102
WO 2004060862	A3	20041125		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ				
AU 2004203788	A1	20040722	AU 2004-203788	20040102
CA 2511856	A1	20040722	CA 2004-2511856	20040102
EP 1581489	A2	20051005	EP 2004-700047	20040102
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2004006618	A	20051206	BR 2004-6618	20040102
CN 1747930	A	20060315	CN 2004-80003468	20040102
JP 2006516557	T	20060706	JP 2006-500146	20040102
ZA 2005005183	A	20060426	ZA 2005-5183	20050627
IN 2005KN01260	A	20061110	IN 2005-KN1260	20050628
MX 2005PA07262	A	20050908	MX 2005-PA7262	20050701
NO 2005003726	A	20050928	NO 2005-3726	20050803
US 2006229254	A1	20061012	US 2006-541387	20060509
PRIORITY APPLN. INFO.:			FI 2003-14 A	20030103

WO 2004-FI1 W 20040102

OTHER SOURCE(S): MARPAT 141:140770

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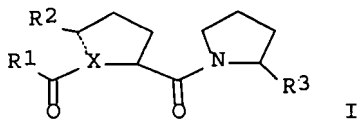


I

AB The invention provides compds. I [X is N or C; R1 is (un)substituted alkyl, alkenyl, a carbocyclic or heterocyclic ring; R2 is H or (un)substituted alkyl, alkenyl or alkynyl; R3 is H, cyano, hydroxy, oxo, halo, alkyl, alkoxy, aryl, aryloxy, arylalkoxy, amino, alkylamino, arylamino, arylalkylamino, cycloalkyl, heterocyclyl, carboxy, acyl, etc., where the alkyl groups may be substituted; when X is N, the dotted line represents a single bond and R2 is not H; when X is C, the dotted line represents a double bond and R2 is H] or their pharmaceutically-acceptable salts or esters having prolyl oligopeptidase inhibitory activity for the treatment of neurodegenerative diseases such as Alzheimer's disease and senile dementia. Thus, 2-(benzylcarbamoyl)cyclopent-2-enecarboxylic acid 2-(S)-cyanopyrrolidine amide was prepd. from cyclopent-2-ene-1,2- dicarboxylic acid 1-Me ester and proline Me ester and showed IC50 = 0.38 nM for inhibition of pig brain prolyl oligopeptidase.

L8 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2003:170639 CAPLUS Full-text

DOCUMENT NUMBER: 138:337715

TITLE: Synthesis of Novel Thrombin Inhibitors. Use of Ring-Closing Metathesis Reactions for Synthesis of P2 Cyclopentene- and Cyclohexenedicarboxylic Acid Derivatives

AUTHOR(S): Thorstensson, Fredrik; Kvarnstroem, Ingemar; Musil, Djordje; Nilsson, Ingemar; Samuelsson, Bertil

CORPORATE SOURCE: Department of Chemistry, Linkoeping University, Linkoeping, S-581 83, Swed.

SOURCE: Journal of Medicinal Chemistry (2003), 46(7), 1165-1179
CODEN: JMCMAR; ISSN: 0022-2623

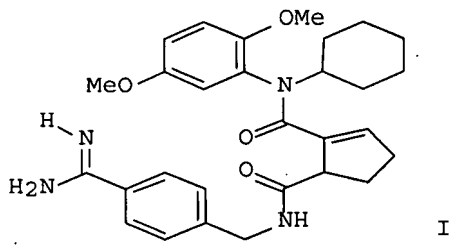
PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 138:337715

GI



I

AB (amidino)benzylaminocarbonyl-substituted cyclopentenylcarboxamides and cyclohexenylcarboxamides such as I are prepd. as human .alpha.-thrombin inhibitors using ring-closing olefin metathesis in the presence of the second-generation Grubbs olefin metathesis catalyst as the key step. .alpha.,.beta.-Unsatd. carboxylic acids undergo ring-closing olefin metathesis in the presence of the second-generation Grubbs olefin metathesis catalyst to provide cyclopentenecarboxylic and cyclohexenecarboxylic acids in 85-98% yields; use of the first-generation Grubbs olefin metathesis catalyst gives no product with the free acids, and gives product in low yields only when the carboxylic acid moieties are reduced. Coupling of the unsatd. acids with either amines or (Cbz-amidino)benzylamine dihydrochloride followed by hydrolysis of an ester substituent and coupling with either (Cbz-amidino)benzylamine dihydrochloride or amines provides .alpha.-thrombin inhibitors such as I. Amidation reactions of the substrate acids with hindered aryl amines only proceed using BOP chloride as the coupling reagent at elevated temps. in DMF; other coupling reagents give products either in decreased yields or not at all. Most of the 5-(amidino)benzylaminocarbonyl-2- cyclopentenylcarboxamides inhibit .alpha.-thrombin with IC50 values of 0.1-10 .mu.M while most of the isomeric cyclopentenylcarboxamides and the cyclohexenylcarboxamides inhibit .alpha.-thrombin with IC50 values between 1-100 .mu.M. The crystal structure of an (amidino)benzylaminocarbonyl- substituted cyclopentenylcarboxamide (IC50 = 220 nM) bound to .alpha.-thrombin is detd.; anal. of the crystal structure led to the design and synthesis of (amidino)benzylaminocarbonyl-substituted cyclopentenylcarboxamides contg. either 3-ethylphenyl or 2,5-dimethoxyphenyl groups with improved binding affinities for .alpha.-thrombin, e.g. I (IC50 = 49 nM).

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> FIL STNGUIDE

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FULL ESTIMATED COST	0.42	380.99

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